Genentech
IN BUSINESS FOR LIFE

DEPARTMENT OF REGULATORY AFFAIRS

1 DNA Way MS#242
South San Francisco, CA 94080-4990
(650) 225-1558
FAX: (650) 467-3198

March 16, 2005

ELECTRONIC AND HAND DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: Docket No. 2004N-0355: Scientific Considerations Related to Developing Follow-on Protein Products

Dear Dr. Galson:

Genentech, Inc. appreciates the opportunity to provide additional comments to the above-referenced docket on scientific topics related to the development of follow-on protein products. We also appreciate the Food and Drug Administration's (FDA's) commitment to having an open public discussion on this complex and controversial issue and applaud the agency for holding a Stakeholders meeting in September 2004 and the February 2005 workshop.

Genentech is hopeful that the scientific discussion and feedback provided will assist the FDA in determining whether the development of a regulatory pathway for follow-on protein products is appropriate, and, if so, what information is required to ensure that the products are safe and effective and share the same high quality as the innovator's products.

On 11 November 2004, Genentech submitted detailed comments to the agency regarding the following scientific issues, which were raised at the September 2004 Stakeholders meeting on follow-on protein products:

- The larger and more complex protein products invariably consist of a family of product-related substances. Thus, the profile for a particular protein product is a unique fingerprint, reflecting the method of production and purification, its stability in the final formulation, and the analytical methods used for measurement. Consequently, each protein product is inextricably linked to the manufacturing process used to produce it. Unlike the comparative capabilities that exist for small molecules, final product specifications for biotechnologically derived products are only one component of the control process used to evaluate protein products. No two biotechnologically derived products manufactured and tested using different processes and methods can be considered the same.
- A change to the manufacturing process or controls can alter the composition or conformational structure of a protein. This can result in a different immunogenicity profile or affect the safety and/or efficacy profile. Even the most sophisticated analytical methods available cannot assess the effect of small differences between two products.
- Comparability does not apply to the comparison of products produced by different manufacturers, using different manufacturing processes and analyzed using different techniques. An essential component of using comparability protocols is the availability of approved drug substance and drug product specifications, as well as sufficient manufacturing science data and experience to demonstrate a thorough understanding of product-specific and process-specific considerations. An innovator can use a combination of product development history, historically established standards, and validation studies to evaluate and compare the results obtained before and after introducing a manufacturing change.
- Prior to approval, head-to-head immunogenicity studies of the innovator's product and the follow-on product should be conducted for all follow-on protein products in each individual patient population to determine whether the immunogenicity profiles of the two drugs are different.
- Confirmation that the innovator's product and the follow-on protein product will have the same therapeutic effects cannot be based on analytical and bioequivalence data due to the complex nature of protein products, and the lack of understanding of the mechanism of action for the majority of products.

We would like to take this opportunity to focus on the following specific issues raised at the February 2005 workshop that were not discussed in our previous response to the Agency.

1. LACK OF PUBLIC REFERENCE STANDARDS AND REFERENCE MATERIALS

At the February workshop, it became clear there exists a consensus that a follow-on protein product should be characterized as extensively as possible using state-of-the-art analytical methods (i.e., physical, chemical, and biological) and shown to be as similar as possible to the innovator's product in accordance with the FDA's definition for follow-on protein products. Although we agree with this principle, the reality is that the drug substance manufactured by the innovator is not a commodity of commerce, and, as such, the reference standards and/or materials prepared, qualified, and used by innovators are not available to follow-on manufacturers. Furthermore, to ensure that a reference material is reflective of lot to lot variability, the reference material is generally composed of a pool of several batches of drug substance.

Moreover, because of the complexity and labile nature of proteins, reverse engineering of biotechnology derived finished products cannot be used to reliably generate drug substance that is reflective of the innovator's material. Therefore, it is questionable whether adequate analytical studies can be used to generate reliable results demonstrating that a follow-on protein product is identical or similar to the innovator's product, qualitatively or quantitatively. As such, Genentech believes these facts further justify the notion that follow-on manufacturers must be required to generate adequate safety and effectiveness data for their products before approval and marketing.

2. PRODUCTS WITH CLAIMS OF MULTIPLE INDICATIONS

As stated previously, follow-on manufacturers need to generate sufficient safety and effectiveness data for their products before approval. The FDA has approved many protein products for the treatment of multiple diseases. However, it is not appropriate to assume confirmation of activity of a follow-on product in a single disease or phase of disease as confirmation of effectiveness across different diseases or phases of diseases. For the following two reasons, Genentech believes separate clinical studies should be performed prior to

approval to demonstrate the safety and effectiveness of each follow-on protein product for the treatment of each disease:

- Because the follow-on manufacturer will use a totally different process (i.e., different cell line, raw materials, manufacturing process, test methods, reference materials, specifications, container/closure system, and manufacturing and testing facilities), a follow-on protein product will never be identical to the innovator's product. A follow-on protein that differs in its physico-chemical and/or biological characteristics can yield different clinical outcomes (safety and/or effectiveness) in different patient populations. For example, products with different tertiary structure or different molecular variants can elicit different immune response in patients with or without an underlying immunological disease.

- In most cases, the mechanism of action for protein products is not known or fully understood. Even if the molecular interactions with the immediate target are identified, there is a cascade of multiple secondary mechanisms of action that may vary across diseases. Moreover, safety signals are likely to vary with type of disease and concomitant medications given to patients. Thus, it is not scientifically valid to assume that the clinical data generated in one patient population applies to another population.

3. INTERCHANGEABILITY ISSUES

In our November 2004 letter to the Agency, we discussed the reasons that follow-on manufactures should perform non-inferiority clinical studies to demonstrate product interchangeability (i.e., therapeutic equivalents). The comments stated previously in Section 1 lend additional scientific support to such a recommendation. In addition, for the reasons stated in Section 2, non-inferiority studies should be performed for each indication for each follow-on protein product.

Again, Genentech appreciates the opportunity to provide input to the FDA and comments to the Docket. While Genentech supports the current FDA process for seeking public input on the relevant scientific issues in question, we encourage the FDA to also seek public input on the myriad legal issues inherent in the development of an approval policy for follow-on protein products. We believe the issues addressed herein are not distinct from several important legal issues and should be addressed concurrently. At the 24–26 February 2005 Generic Pharmaceutical Association's annual meeting in Boca Raton, Florida, Acting Commissioner, Lester Crawford, said that the FDA is "preparing for processing this [follow-on proteins] new category of products" and intends to develop several guidances and concept papers. Dr. Crawford mentioned the development of draft guidances, including an immunogenicity guidance and a chemistry guidance, based on information received at the 14–15 September 2004 Stakeholders meeting and the 14–16 February 2005 Drug Information Association/FDA workshop. Unfortunately, Dr. Crawford made no mention of the timing to address the legal issues raised or the legal implications on the content and scope of any guidance document for follow-on protein products. It is not possible to generate a meaningful discussion of immunogenicity and chemistry or any other scientific considerations until the legal issues are resolved, specifically the protection of the innovator's proprietary information and the establishment of requirements for designating reference material.

We strongly urge the FDA to commit to an equally robust public discussion regarding the treatment and use of confidential commercial and trade secret information before moving forward with developing and publishing any draft guidance documents relating to follow-on protein products.

Sincerely,

R. Robert L. Garnick

Robert L. Garnick, Ph.D.
Senior Vice President
Regulatory Affairs, Quality, and Compliance
Genentech, Inc.

Docket-019 ao